

PHYSIOLOGICAL ASPECTS OF GENETICS

BY SEWALL WRIGHT

Department of Zoology, The University of Chicago, Chicago, Illinois

It is appropriate to begin this review by calling attention to the posthumous appearance of "The mutants of *Drosophila melanogaster*" by C. B. Bridges, completed and edited by Katherine S. Brehme (1). While not explicitly physiological, the type of work of which this monograph is the culmination underlies all physiological genetics and is of the greatest significance in its implications.

Multiple alleles.—Inspection of the descriptions of the *Drosophila* mutations brings out well the justification for the conventional concept of the gene, as a first approximation. Multiple alleles are known at a large proportion of the loci. Allelic mutations are usually much alike, differing mainly in degree of divergence from type. Dominance is usually correlated with order of effect and the compounds of two recessive alleles are usually intermediate. In contrast, there is little or no tendency toward resemblance in the effects of neighboring nonallelic mutations. There are, however, interesting exceptions to these rules, some of which are being studied intensively for their implications with respect to the nature and physiology of the gene.

Stern (2) and Stern & Schaeffer (3) have made such a study of certain cubitus interruptus alleles and find that two independent variables are required to account for effects on even a single criterion, venation. They postulate that all of the alleles control the transformation of a single substrate into a single product, but analyze this into two steps in which alleles may differ independently: power of combining with substrate, and rate of formation of the product. The reaction must be noncatalytic to permit independence, since if the ratio of gene (or gene controlled agent) to total amount of substrate is small, there can be no effective differences in competitive power. Under the otherwise less plausible hypothesis that a common substrate may be transformed into somewhat different immediate products with different efficiencies relative to the observed character, substrate transforming power and product efficiency may be quite independent even with catalytic action (4). With a single immediate product of all alleles, effects on different characters should be parallel (except for thresholds). This is not

necessary if there are different immediate products. It turns out that there is no parallelism in the effects of the *ci*-alleles on venation, crippling of the legs, and tendency to extra bristles.

Other exceptional cases can be accounted for by postulating that alleles may differ with respect to which of a group of related substrates they are able to transform. If the products affect the same observed character, completely recessive alleles may have the same or similar effects and yet reconstitute the dominant type in their compound as in several cases in *Drosophila melanogaster* (1).

Whiting (5) suggests that sex determination in *Habrobracon* (and probably other hymenoptera) may rest on a mechanism which may be interpreted as of this sort. He has demonstrated a series of at least nine alleles. The ordinary haploid males may carry any one of these, yet are alike phenotypically. Homozygous diploids of all sorts are also males, indistinguishable from each other, while all kinds of heterozygotes are phenotypically similar females. Whiting postulates a chromosome segment within which crossing over does not occur and which contains numerous sex genes. The various "alleles" are held to consist of different combinations of dominants and recessives with consequent complementary effects in heterozygotes. This general scheme may be illustrated by postulating that each "allele" has one positive component ($A_1a_2a_3$ — A_9 , $a_1A_2a_3$ — A_9 , etc.), that each positive component acts on a somewhat different substrate which is sufficiently limited in amount to permit dominance, and that all of the products are equivalent in switching sex differentiation. In haploids and homozygotes the ratio of A components to other genes would always be 1 to 1; in heterozygotes, always 2 to 1, giving a mechanism of sex determination analogous to that familiar in other animals. There is, however, the alternative view that femaleness may be attributed to a reaction to the introduction into the egg of a foreign antigen.

More generally, there may be two or more substrates which multiple alleles act upon with different relative efficiencies. Here there would be competition of two substrates for the same gene as postulated for the C series in guinea pigs (4). There may also be partially complementary effects as in the brachyury series of the mouse, discussed later (6). Oliver & Green (7) find such a situation in effects of lozenge alleles of *Drosophila* on viability and fertility. Jones (8) finds that mutations that arise from time to time in long

selfed lines of corn tend to have a complementary effect (heterosis) when crossed to the parent type as if the mutant acted more efficiently than the latter in some respects but less efficiently in others. Stadler & Fogel (9, 10) and Silow & Yu (11) describe partially complementary effects in extensive series of multiple alleles affecting color in corn and cotton respectively.

The difficulty indicated above in making a sharp theoretical distinction between allelism and complete linkage in certain cases has been enhanced by the discovery of cases in which rare crossing over occurs between genes that would otherwise be considered as alleles because of the type of interaction in compounds (7, 12). It seems probable that there may be longitudinal replications of pattern within the gene and that these tend to drift apart in physiological properties, under a well known evolutionary mechanism, ultimately becoming separate genes subject to crossing over and complete separation by chromosome breakage and rearrangement. It does not appear practicable to limit the term gene to ultimate self-duplicating entities (if these are distinguishable at all). Practically the boundaries of the gene become a matter of convenience: a block of self-duplicating material of a chromosome which is not subject to crossing over or chromosome breakage.

Position effect.—Position effect has long been recognized as a phenomenon which should throw light on immediate gene physiology. Stern & Heidenthal (13) have obtained results in *Drosophila melanogaster* that pose a problem for any theory. They used translocations R(*ci*) between chromosomes III and IV, involving cubitus interruptus and between chromosomes I and IV, involving a dominant type allele R(+). Genotype R(+)/*ci* had interrupted veins (reduced dominance of type) confirming Dubinin & Siderov who also had found R(+)/R(+) and Haplo R(+) to be normal. Genotype +/R(*ci*) also had interrupted veins and *ci*/R(*ci*) was more extreme than *ci*/*ci*. The authors give alternative interpretations of these results but note the difficulty of fitting these to another observation, that R(+)/R(*ci*) is usually normal.

Ephrussi & Sutton (14) discuss the difficulties with the usual interpretations of position effect, and suggest that it is a result of stress near the affected loci due to changed conditions of pairing of homologs. The obvious difficulty with this hypothesis in cases of position effect in homozygotes and hemizygotes they account for as due to stress resulting from the tendency toward nonhomologous

pairing of heterochromatin, thus bringing in the well known relation between position effect and proximity to heterochromatin. As they note, however, the disappearance of position effect in heterozygotes between different translocations, illustrated above, is not easily accounted for.

Sutton has published instructive analyses of position effects at the Bar locus and of relations between breaks and phenotypes in the yellow-scute region of *Drosophila melanogaster* (15, 16). Roberts (17) gives an exhaustive statistical analysis of the characteristics of thirteen reciprocal translocations in corn for possible position effect. There were slight differences from type in both heterozygotes and homozygotes.

The nature of the difference between heterochromatin and euchromatin continues to attract attention (18, 19, 20). The idea has been developed that heterochromatin consists of regions in which the same gene is duplicated many times. This is correlated with the idea that it consists of genes which have to do with mass products (nucleic acid, tissue protein), in contrast with ones concerned with products such as enzymes required only in small amount. It has also been associated with multiple factor heredity (21) although it should be noted that the latter requires similar effects in different chromosomes (or at least in widely separated loci) rather than duplications in one region.

There is, however, some question of the criteria for heterochromatin. Muller (22) distinguishes between "blocks" which make up a large portion of the length of the mitotic X-chromosome of *Drosophila melanogaster* but relatively very little in the much larger salivary chromosomes, and the residual heterochromatin. He finds the former virtually unbreakable under x-ray treatment, the latter much more breakable than euchromatin.

Chromosome chemistry.—Mirsky & Pollister (23, 24) have described methods of extracting a nucleoprotein, consisting of highly polymerized pure desoxyribose nucleic acid in loose combination with basic protein, which is wholly protamine in nucleoprotein from mature sperm of trout, but wholly histone in that from blood cells and liver cells. The yields are roughly proportional to size of nucleus and range upward to 90 per cent of the dry weight in the case of trout sperm suspensions. Mechanically isolated chromatin threads assayed nearly 100 per cent nucleoprotein. Claude & Potter (25) describe similar results for rat leukemic cells.

Stedman & Stedman (26) report results that seem to be in serious disagreement with this account. They find an acid protein more complex in amino acid content than histone and protamine, as a major constituent of cell nuclei, including those of fish sperm. According to them, this protein which they call chromosomin, is responsible for the characteristic staining reactions of nuclei. They estimate cod sperm to contain 28 per cent nucleic acid, 12 per cent histone, and 60 per cent chromosomin.

Schultz & Jose (27) note differential staining reactions of the bands and interbands of *Drosophila* salivary chromosomes which must be attributed to protein differences rather than to the differences in nucleic acid content.

The most suggestive recent result bearing on gene chemistry comes from work on bacteria, which have no clearly recognizable chromosomes. Type specificity in pneumococcus depends on a polysaccharide capsule with very strong antigenic properties. It was shown many years ago that specificity could be removed (e.g., by treatment with antiserum), giving "rough" unencapsulated strains, with a tendency to relapse to capsule production, always of the original specificity. Means of transforming type by use of extracts from dead bacteria of the desired type were, however, discovered. Avery, MacLeod & McCarty (28) have now obtained the active principle of such extracts in apparently pure form by fractionation methods. It turns out to be a polymerized desoxyribose nucleic acid, molecular weight about 500,000, lacking type specific carbohydrate and protein as indicated by very sensitive serological tests. Yet it can induce an unencapsulated pneumococcus derived from one type to produce thereafter the specific carbohydrate of the type from which the nucleic acid has been derived as well as more nucleic acid with this property. The great possible significance of this observation in the interpretation of the role of the nucleic acids of chromosomes and of other self-duplicating entities is obvious.

Induction of mutation.—We may note first a paper by McClintock (29) on the systematic production of small, haplo-viable deficiencies in corn by providing the conditions for mechanical breakage (chromosome bridge and breakage-fusion cycle).

The induction of gene mutations by ionizing radiation has been variously attributed to the direct effects of single ionizations or activations, effects of clusters, and indirect effects, more or less

remote from the site of the "hit." Zimmer & Timofeeff-Ressovsky (30) present additional data from the use of x-rays and neutrons on *Drosophila* from which they conclude that ion clusters may be excluded as the primary events (frequency of these per unit dose increases 30 per cent in the range from 10 kv. x-rays to γ -rays while mutation rate is constant). Fano (31) in a theoretical discussion concludes that this independence of wave length does not warrant the conclusion that mutation is a direct and invariable consequence of a hit within a postulated definite sensitive volume of a gene. Giles (32) and Fano (33) add corroboratory data for the conclusion that neutrons are only about half as effective as x-rays per unit of energy absorption in inducing recessive lethals in *Drosophila*. This favors the view that the diffusion of effects is at least not so great as to prevent wastage of ionizations in the dense ionization tracks found with neutron bombardment.

Giles (32) also adds to the data indicating that neutrons are considerably more effective than x-rays in breaking *Tradescantia* chromosomes and that the frequency of all types of rearrangement rise only linearly with dosage. Fano (33) finds the same for breakage of *Drosophila* chromosomes. Similar results are also found for dominant lethals by Demerec & Fano (34) who note that this is in harmony with Pontecorvo's suggestion that these are largely isochromatid rejoins. The rise of gross aberrations linearly with dosage and absence of any differential effects of duration or intermittency of treatment in the case of neutrons (32), contrast with the results of x-ray treatment (35) under which gross aberrations increase as the square of the dosage if duration of treatment is constant, but less rapidly under other conditions, in such a way as to indicate rapid loss of capacity of broken chromosome ends to rejoin. The new results thus strengthen Giles' hypothesis that it requires a cluster of ionizations to break a *Tradescantia* chromosome and that most double breaks under neutron treatment are due to single ionization tracks. Lea & Catcheside (36) present a thoroughgoing attempt to reach a quantitative theory for breakage of *Tradescantia* chromosomes. They estimate the mean period of "healing" of broken chromosome ends to be about three and a half minutes. They are led to the conclusion that the chromosome must be traversed by about seventeen ionizations in order to break. An isochromatid break requires traversal of both chromatids by a single track. Traversal of separate chromatids which may

be up to 1 or 2 μ apart, by the same track should theoretically be the most frequent cause of gross aberrations, which would account for the linear relation to dosage. Their hypothesis that traversal by any proton track should result in a break is not, however, in harmony with an observation of Giles (32) that neutrons with energies up to only 7.5 mev are more efficient than ones with energies up to 15 mev and thus with less dense tracks.

In the case of x-radiation, Lea & Catcheside estimate that wave length 4.4 Å should be most efficient in producing the requisite number of ionizations in a path of sufficient length to traverse a *Tradescantia* chromosome. Efficiency should fall off rapidly with greater wave length, becoming almost nil at 6.4 Å (too short a track) and should also fall off with wave lengths less than 4.4 Å because of insufficient density of ionization in all but the tail of the path of the secondary electron. Efficiency should not change much below 2 Å, however, because of probable approximate constancy per unit dose of tertiary clusters of requisite size. In a later paper (37) they confirm these predictions, obtaining maximum chromatid and isochromatid breakage at 4.1 Å, less at 1.5 Å and 0.15 Å, and least at 8.3 Å.

Koller & Abend (38) find no single breaks and a deficiency of odd numbered breaks in x-rayed sperm of *Drosophila*. Kaufmann (39) describes a larval female *Drosophila* (father x-rayed) with at least 32 breaks detectable in the salivary chromosomes. Fano (40) discusses the mechanics of induction of gross rearrangements in *Drosophila* sperm. He stresses the effects of one union on others, after union begins following fertilization. McClintock (41) describes a case in which there was union in the zygote of ends of chromosomes broken in the male and female gametophytes respectively. Sax (42) finds that centrifugation during x-radiation of *Tradescantia* microspores increases the frequency of aberrations. Colchicine treatment prior to x-radiation on the other hand was found by Brumfield (43) to cut down the rate of chromatid aberration.

While evidence is accumulating that chromosome breakage by ionizing agents requires a cluster of ionizations, it is also clear that it can occur under ultraviolet treatment, without ionization. The mechanisms however are clearly different. Ultraviolet produces only single deletions to an appreciable extent, while x-rays produce all types. Swanson (44) confirms these conclusions and

finds that treatment of pollen tube nuclei of *Tradescantia* by ultraviolet tends to inhibit the production of aberrations by x-rays an hour later. Treatment by ultraviolet an hour after x-radiation inhibits single deletions. It is suggested that ultraviolet has an effect on the matrix favoring restitution. Kaufmann & Hollaender (45) find that ultraviolet, and also near infrared, following x-radiation of male *Drosophilas*, reduces aberration rate.

The evidence from various organisms that the most effective wave length of ultraviolet in inducing mutations is about 2650 Å (where the strong absorption band of nucleic acid is located) is extended by experiments on spores of *Penicillium notatum* (46).

Gene *a* of corn (colorless aleurone) is ordinarily a stable recessive. In the presence of *Dt* it mutates freely to a dominant allele, *A*. Stadler (47) finds that x-rays produce no mutations of *a* (in *aa dt dt*) with doses capable of yielding about 900,000 losses or inactivations of *A*.

Mampell (48) describes a gene in *Drosophila pseudoobscura* that causes a general increase in mutation rate, 35-fold when heterozygous, twice this when homozygous.

Such genes as these presumably act through chemical channels. Direct attempts at inducing mutations by chemical treatment continue largely disappointing. Treatment of eggs or larvae of *Drosophila melanogaster* with deuterium (49) and with proteolytic enzymes (50) gave no detectable increase in lethal mutations. A study of the effect of copper sulphate and high pH on the rate of mutation of the unstable gene *mt-3c* of *Drosophila virilis* gave an effect but in the direction of decrease (51).

Mutations in unicellular organisms are attracting increased attention. Luria & Delbrück (52) find that the statistics of occurrence of resistant clones of colon bacteria on treatment with a bacteriophage indicate chance mutation (rate 0.32×10^{-8} per bacterium per division cycle) rather than a directed response. Spiegelman, Lindegren & Hedgecock (53) have studied adaptive fermentation of galactose by yeasts. A technique for observation of individual cells revealed that in a nonadapted haploid strain adaptation was a matter of individual mutation. A culture became adaptive only by selection in an increasing population. But in a particular diploid strain, 100 per cent adaptation occurred abruptly without cell multiplication after a lag of three hours. Other diploid strains did not develop adaptive enzymes.

Sturtevant (54) discusses the likelihood of specific induction of mutations by serological methods in view of the direct relations between gene and antigen. Emerson (55) describes tests of this hypothesis with *Neurospora*. Antisera produced 25 variants in 695 treated lines (0 in 276 controls) of which at least 11 were found to be simple Mendelian. The evidence indicated induction rather than selection.

Transformation from one type of pneumococcus to another by means of extracts from the latter has already been discussed (28). The results suggest chemical isolation and transfer of a gene rather than induction of mutation.

Genes and antigens.—The likelihood that the specificity of antigens reflects that of genes more directly than does any other character makes progress in this field of special interest in physiological genetics. The Rh series of antigens of human red blood cells has been the object of intensive study recently. One pair of alleles (*Rh*, *rh*), independent of those responsible for the A, B, O, and M, N antigens is indicated where the criterion is agglutination by a particular antiserum (56). By testing each individual of a family with several different antisera, however, there is evidence for at least six alleles (57, 58). Each of three of these, *Rh₀*, *Rh'*, *Rh''* [Wiener's revised terminology (59)], determines a distinct specificity. Two others, *Rh₀'* and *Rh₀''*, combine the specificities indicated by subscript and superscript while *rh* was not responsible for any positive reaction to the test sera. Heterozygotes exhibit all of the positive effects of the two genes. Other sera have been obtained which reveal agglutinins determined by some at least of the class of alleles called *rh* (60, 61).

The number of antigens found in the red blood cells of cattle has reached about 40, according to Stormont, Irwin & Owen (62). Here as in man there is evidence for multiple alleles with compound specificities.

Irwin & Cumley (63) have continued their studies of the genetics of antigens in the red blood cells and serum proteins of numerous species of pigeons and doves and their hybrids, bred by Cole. The common and specific cellular antigens of eleven species of *Columba* form an interlocking pattern with only slight group differentiation of old and new world species (64, 65). A study of the serum antigens of the Senegal dove, absent in the Ring dove, was carried to the fourth back cross to the latter (66). Segregation of

at least three (probably four) independent antigens was established. These were independent of the ten cellular antigens differentiating Senegal from Ring dove. It is noted briefly that pigeon-dove crosses gave results that indicated intraspecific as well as interspecific differences in genes determining serum antigens. Two species of duck, the Mallard and Muscovy, are found to have specific as well as common red blood cell antigens [McGibbon (67)]. Their sterile F_1 hybrid has most of the parental antigens but also a new hybrid antigen, analogous to those of certain Columbidae hybrids. A Muscovy male proved to be heterozygous for two alternative antigens both absent in the Mallard.

It has long been established that a hostile reaction to a transplanted tissue usually depends on the presence in the latter of dominant genes, presumably determining antigenic specificities, that are not present in the host. Specificity genes of the host, absent in the graft, are of little or no significance. Results of transplants within and between two distinct inbred strains of rats, previously reported by Loeb & King, could only be reconciled with this theory on the hypothesis that these strains had remained heterozygous in spite of 67 generations of brother-sister mating. Data from generations 91 to 106 now show an approach to the expected tolerance of transplants within strains, with lack of tolerance between (68). But unexpected tolerance of grafts from individuals derived from a recent cross between the two lines raises a new difficulty.

Self incompatibility in plants is probably related to these specificity reactions. Most cases involve only one locus with numerous alleles. There is inadequate growth of pollen with an allele present in the style. The great number of such alleles at one locus is illustrated by recent studies of Atwood on white clover (69). In one small highly isolated population 36 of 49 tested alleles proved distinct. In another larger isolate, 39 of 49 were distinct.

Tetraploids from self sterile diploids behave differently in different cases. Homozygous pollen (e.g., S_1S_1) seems always to be inhibited by presence of the same gene in the style, but with heterozygous pollen (e.g., S_1S_2) the inhibition tends to be reduced to varying extents. In *Oenothera organensis* (self sterile) the tetraploids are still self sterile but the growth of heterozygous pollen tubes, especially of certain genotypes, is much greater than that of homozygous pollen tubes (70). In *Oenothera rhombipetala* pollen is also successful only if both its S-genes are foreign to the style

(71). Tetraploids from self sterile pears on the other hand are self fertile. Heat shock of the pollen mother cells of diploids, followed by selfing, results in triploid fertile seeds (72). Atwood (73), working with white clover, finds a more complicated situation. Two tetraploids were self sterile but crosses between them yielded 26 self compatible to only 3 self sterile clones. Practically all possible tests of cross pollination between these clones were made and gave results which the author interprets on the hypothesis that the presence of two or more kinds of heterozygous pollen (possible in trialleles such as $S_1S_1S_2S_3$ and tetraalleles $S_1S_2S_3S_4$) favors pollen tube growth, which thus is assumed to depend on the reaction between stigma and all of the pollen placed on it. There are, however, as he notes, serious discrepancies under this hypothesis. The results can be explained qualitatively better by the hypothesis of Lewis (70) that there are great differences between the reactions of different kinds of heterozygous pollen tubes in seemingly similar situations.

The phenomena associated with mating types in ciliate protozoa appear somewhat similar to those of self sterility in plants (74). In *Paramecium*, conjugation ordinarily occurs only between different mating types of the same species and variety. Mendelian segregation occurs but the phenomena are complex. There is a very different situation in *Euplotes patella*. Kimball (75) finds six types based on the possible combinations of three alleles, mt^1 , mt^2 , and mt^3 . Each gene, acting independently in heterozygotes, appears to be responsible for secretion of a specific substance which induces conjugation in any genotype which lacks the corresponding gene. Thus fluid from heterozygotes induces conjugation within clones of the five other types while fluid from homozygotes does this for only three of them. Powers (76) finds that mating type in clones of double animals is determined by the independent action of the genes of both nuclei, which may be different.

In higher animals a rather high degree of self sterility is found in tunicates. Morgan (77) presents data bearing on the genetics and physiology. The block is in the egg membrane (a diploid product) and can be overcome by rupture or treatment with acid. There is clearly a genic basis but the phenomena are complex. It is held by the author that cross sterility, exceedingly rare between random individuals and not very frequent even among progeny of one individual, depends on close similarity (demonstrably not always

identity) with respect to genes in several extensive multiple allelic series. The natural self fertility (of about 5 per cent of wild individuals) is attributed to differences in the germ tract due to mutable genes. One-way cross sterility is commoner than reciprocal. This is easily explained, as noted, if sperm specificity is under control of the haploid nucleus, but no other case of action of the sperm nucleus is known. If under diploid control, it calls to mind the asymmetry in human blood group reactions.

Genic control of metabolic processes.—Rapid progress has been made in the analysis of genic control of metabolic processes of the mold, *Neurospora*, by Beadle, Tatum, and associates (78). This organism is admirably adapted to determination of genes and their relations by the possibility of growing separately all of the products of the reduction division (ascospores from the same ascus) following a cross.

Type *Neurospora* can be grown on a medium containing no other nutrients than inorganic salts, a simple sugar, and biotin (79). In these experiments (78), perithecia or conidia are treated with x-rays or ultraviolet light to induce mutations. Single spore cultures are then grown on a medium designed to supply any necessary diffusible substance which a mutant may have lost the capacity to synthesize. Normal growth on this medium, but failure of subcultures on the basic medium, indicate such a mutation. Trials with progressively simpler supplements to the basic medium have usually led to the discovery of a single substance (or any one of a group of closely related substances) as all that is needed as a supplement to restore full growth. Among such substances, each effective with a particular mutation, are several amino acids (78, 80, 81), e.g., arginine, methionine, tryptophane, lysine, valine, leucine; several vitamins (78, 82), e.g., thiamine, nicotinic acid, pantothenic acid, *p*-aminobenzoic acid, pyridoxine, choline; and pyrimidine nucleosides, uridine or cytidine (83). There have often been recurrences of what appear to be exactly the same mutation. In several cases, however, what at first appears to be a recurrence has turned out to involve inactivation of a different link in the chain of processes leading to the supplement in question. Thus one mutant will grow if either thiamine or thiazole is added to the basic medium. Another will grow on addition of thiamine but not with either thiazole or the pyrimidine constituent as the supplement (78). The interpretation is that a step in the synthesis of

thiazole fails in the former, the final step in the synthesis of thiamine from its constituents in the latter. Similarly (78) one "methionineless" mutation can utilize homocystine or cystine as well as methionine, while another cannot add the methyl group to homocystine to produce methionine. The "tryptophaneless" mutations (84) can utilize indole [to combine with serine to form tryptophane (85)] as well as tryptophane itself but one type can also utilize *o*-aminobenzoic acid while another cannot.

The most extensive chain analyzed concerns fifteen mutations which grow normally with arginine as the sole supplement (86). Four nonallelic members of this group also grow normally with either ornithine or citrulline as the supplement. Presumably these determine four different steps in the synthesis of ornithine. Two nonallelic mutations which can utilize either citrulline or arginine but not ornithine presumably control two different steps in the synthesis of citrulline from ornithine (which involves taking up of ammonia and carbon dioxide with loss of water). One type of mutation can utilize only arginine, which is derived from citrulline by taking up of another molecule of ammonia (with loss of water). Other mutations appear to be exact recurrences. Finally, arginine can be hydrolyzed into ornithine and urea (87), as in the ornithine cycle of mammals.

It is possible to study dominance in spite of the haploid state of the nuclei, by allowing the syncytial hyphae from two mutations to fuse to form a heterocaryon in which the nuclei from the two sources freely intermingle (88). In most cases, each kind of nucleus is able to carry through the metabolic steps in which the other fails to a sufficient extent to permit normal growth. There is often indeed a wide factor of safety. Thus tests indicated that the ratio of "pantothenicless" to "nicotinicless" nuclei might vary between 1 to 3 and 5 to 1 without disturbance of normal growth. On the other hand, certain morphological mutants that by themselves grew only about 1 per cent as rapidly as wild type gave heterocaryons that still grew only about half as rapidly as wild type, a fact indicating that there is no ratio of nuclei attainable by natural selection, in which both nuclei are adequate. Such mutations may be considered semidominant.

A physiological test for identity (or at least allelism) of two apparently similar mutants can be made by forming a heterocaryon and determining whether there is complementary action.

Thus two kinds of "nicotinicless" complement each other (88).

A substance that improves growth is not necessarily one whose synthesis is interfered with in the mutant in question. Thus a mutant "cholineless" grows normally from the first with choline (or lecithine) as supplement (89). There is some growth however with the unrelated substance methionine (in relatively large amounts) as the only supplement and much improvement if this is added to inadequate amounts of choline. These results are interpreted on the hypothesis that the mutation blocks only the synthesis of choline but that one of the uses of choline (probably that of supplying methyl groups) is relieved by addition of an excess of methionine.

In some cases it has not been possible to alleviate the metabolic defect due to a mutation by any single substance. Thus one mutation grew normally with a mixture of 70 to 80 parts of valine, 30 to 20 parts of isoleucine, but hardly at all (at first) with less than 5 per cent or more than 70 per cent isoleucine in the mixture (80). Either of these amino acids but not both could be replaced by their keto-acid analogs. Neither of the hydroxy-acid analogs were effective. Yet leucine or either its keto- or hydroxy-acid analog could largely replace the valine. Certain amino acids (phenylalanine, norleucine, and norvaline) were strongly inhibitory. Presumably one link in a network of processes is blocked but no simple interpretation has been found.

In this case and in certain simpler ones, a mutant that grew hardly at all at first on the basic medium gradually acquired the capacity to grow at a normal or nearly normal rate. The adaptation is not transmitted to the conidia.

An interesting application of these results has been in the bioassay of certain substances: *p*-aminobenzoic acid (79), choline (89), and leucine (90).

Isolated examples of genic control of simple metabolic processes, in some cases associated with presence or absence of demonstrable enzymes, have been described in other organisms. Sawin & Glick (91) find that the blood of some, but not all, rabbits contains an enzyme capable of destroying atropine and related substances. The presence of this atropinesterase was demonstrated to depend on an incompletely dominant gene. Corkill (92) and Atwood & Sullivan (93) agree on two independent genes as concerned in the production of cyanide by white clover. One dominant gene

determines the presence of cyanogenic glucosides (lotaustraline, linomarine) while another dominant gene determines the presence of a hydrolytic enzyme, linamarase.

In other one-factor cases, the metabolic effect is less easily located. Thus Weiss (94) finds a one-factor difference in soy beans between strains that are normal (dominant) and ones that are chlorotic on calcareous soils. In nutrient solutions, the recessives become chlorotic when the concentration of available iron is low. Their tissues showed relatively high pH, low potassium concentration, high total iron content, but low soluble iron.

In other cases, metabolic differences are due to multiple factors. An example is percentage of sucrose in sugar beets which gives multiple factor heredity with no evidence of a matroclinous tendency after crosses (95, 96).

Ephrussi has reviewed the extensive studies on the relations of genes to the physiology (97) and chemistry (98) of eye pigments of *Drosophila*. This work has related largely to effects on diffusible substances. Ephrussi & Herold (99) describe techniques for the extraction and quantitative estimation of the red and yellow pigments as a basis for the study of the effects of the eye color genes which have not been adequately attacked by the earlier methods. Caspari (100) finds a higher tryptophane content in recessive red eyed *Ephestia kühniella* (aa) than in the dominant black eyed form (a⁺). Other evidence indicates that tryptophane is a precursor of the diffusible a⁺ substance which in turn is a precursor of the pigment. In another paper (101) he describes a new gene which affects testis color autonomously in contrast with the non-autonomous effect of a⁺ on testis as well as eye pigment. Brehme & Demerec (102) give a survey of the effects of the eye color genes on testis color in *Drosophila melanogaster*. There are interesting cases of nonparallelism even within the same series of alleles.

Attention may be called to recent reviews on the embryology of vertebrate pigment cells by DuShane (103, 104) as furnishing a background for interpretation of genetic data on pigmentation. Willier & Rawles (105) describe experiments in which melanophores from cross bred fowl embryos (Rhode Island Red ♂ × Barred Plymouth Rock ♀, the latter with dominant sex-linked genes for barring and silver and an autosomal dominant for black, all lacking in the former) were grafted on White Leghorn embryos. The melanophores of males (barred) and of females (black-red

stippled) both developed autonomously in host feathers irrespective of the sex of the host. The relative frequency of differentiation of female melanophores into black and red pigment cells was found to depend partly on genic modifiers in the donor and partly on the physiological properties of individual feather germs of the host (position in the regional gradient, growth rate, etc.). The barred pattern given by the male grafts was also affected by the properties of the host feather germs. It is noted that differences in the form and size of the black and red granules indicate two directions of differentiation rather than a sequence, arrested in one case. Nickerson (106) describes the results from grafts characterized by two different kinds of barring: sex linked barring of Plymouth Rocks in which the pattern has a period of five or six days, and autosomal barring of Silver Campines in which the period is only about half as long. Both rhythms were maintained in the feathers of White Leghorn hosts, a fact indicating that the periodicity is intrinsic in the melanophores. The melanophores in a given feather obviously do not, however, act independently of each other. It appears probable that regulation occurs through diffusible inhibitory substances produced by the melanophores.

Light is thrown on the immediate cause of differentiation into black and red melanophores by experiments by Wang (107). He finds that autotransplants of whole feather papillae (dermis plus epidermis) from one tract to another produce feathers of the same type and pigmentation as if left undisturbed. Transplants from papillae in which the epidermis has been destroyed produce feathers of the type and pigmentation of the host tract (which furnishes new epidermis to the papilla). The dermal component is necessary as the inductor of the feather and determines its orientation but type and pigment differentiation depend on tract specificity of the epidermis. Foulks (108) has shown that melanophores do not maintain themselves in the papilla but must be continually supplied from the subepidermis. Wang's results thus seem to require that they are not differentiated as to tract until coming under the influence of the epidermal component of the papilla. Transplantation of papillae between breeds (109) invariably yielded feathers of host tract specificity and pigmentation. The epidermal component of the papilla is believed to be wholly lost as a result of breed incompatibility. The melanophores must trace to the host

subepidermis rather than to the grafted dermal papilla in agreement with Foulks' observations.

The effects of various genotypes of the mouse on size, shape, color, and abundance of pigment granules is described briefly by Russell & Russell (110). Harmon & Case (111) describe the effects of several genotypes of the guinea pig on eye pigmentation. Bohren *et al.* (112) give histologic and photometric comparisons of various pigments of the fowl. Baker & Andrews (113), and Ginsburg (114) give photometric comparisons of black and yellow in the guinea pig. It is agreed that the absorption curve for yellow is steeper than that for black in both fowl and guinea pig but whether this implies a chemical difference or merely a difference in colloidal state is not clear.

Ginsburg (114) describes the effects of colorless extracts obtained from the skins of young guinea pigs of diverse genotypes in producing artificial melanin from dopa. An inhibitor was easily demonstrated especially in extracts from white skin (whether of albinos or spotted). This was removable by scraping the skin and thus appeared to be in the epidermis. The extracts from certain genotypes contained an active principle probably a polyphenol oxidase. The potency of extracts from different phenotypes depended on the genic modifiers of yellow present (C series, F, f) regardless of whether the hair was black or yellow, except that it was greater in blacks than in the corresponding yellows. It is concluded that the technique used yields only an enzyme specific for yellow pigmentation.

Extrachromosomal heredity.—The question of possible autonomy of cytoplasmic components is important. The usual criterion is a difference in reciprocal crosses, maintained for at least two generations. Harvey (115) describes the plutei from four echinoderm crosses as almost wholly maternal. But as only the first generation could be produced, it is impossible to decide between cytoplasmic heredity, maternal influence, and determination by products of the egg nucleus before fertilization. Moreover in one of the cases (*Strongylocentrotus purpuratus* ♀ × *S. franciscenus* ♂) a statistical study of the more important form indices by Moore (116) indicates that the hybrid actually is almost exactly intermediate, although necessarily like the maternal species in absolute size.

Russell & Green (117) note briefly a marked matroclinous difference between reciprocal hybrids of two inbred strains of mice which differ in number of lumbar vertebrae (usually five and six respectively). The difference did not persist in large F_2 generations and thus was presumably due to maternal influence.

Gowen (118) has studied the influence of the various chromosomes and possible extrachromosomal materials on the heterosis found in crosses between inbred strains of *Drosophila melanogaster* of different geographic origin. No extrachromosomal effect was indicated.

An immediate effect of recessive mutations on the microspores (haploid) of diploid *Tradescantia* has been found by Rick (119) by x-radiation shortly after meiosis. There was increased variability, decreased size, and increased percentage of abortion. Similar treatment of autotetraploid species showed no significant effects.

Drosophila virilis and *D. americana* differ markedly in many respects. Stern, Schaeffer & Spencer (120) have shown by carefully controlled back-crossing for many generations that no appreciable portion of this difference is transmitted along the straight female line.

There are, however, other cases in which extrachromosomal heredity is indicated. Michaelis (121) describes experiments designed to carry further the analysis of deleterious interaction effects of persistent cytoplasmic components of *Epilobium hirsutum* with genes from other strains of *E. hirsutum* or another species, *E. luteum*. Villerts (122) describes differences in reciprocal crosses in the genus *Begonia*.

Most known cases of apparent extranuclear transmission are concerned with chlorophyll deficiencies in certain species of plants. An important new result in this field is one obtained by Rhoades (123) in connection with white striping of corn due to the recessive gene *ij* (*iojap*). The cross $IjIj \text{ } \varnothing \times ijij \text{ } \sigma^7$ produces only green offspring in F_1 . The reciprocal cross produces white and striped seedlings as well as green ones. Sometimes all seedlings from an F_1 ear are white. The cross, striped $Ijij \times$ unrelated $IjIj$, sometimes produces only green plants, in other cases green striped and white, and occasionally 100 per cent white although in the last case half of the seedlings should be $IjIj$. It appears that in genotype $ijij$ there is a tendency toward mutation in the plastids and that mutants continue to multiply as of the deficient sort and to be

transmitted as deficient plastids along the straight maternal line in spite of restoration of the nucleus to homozygous normal.

There is at least a certain formal similarity between this observation and a series of remarkable results obtained by Sonneborn (124) with *Paramecium aurelia*. The most thoroughly analyzed case concerns a strain in which the individuals secrete a substance that kills individuals of other strains in the course of forty-eight hours. Conjugation can be obtained between the two strains. The descendants of the killer exconjugant remain killers as long as there is no nuclear reorganization. Those of the sensitive exconjugant remain sensitive. Since conjugation results in identical micronuclei and degeneration of macronuclei with reformation from the micronuclei, these results seem to indicate extranuclear heredity. Autogamy, however, results in segregation of killer and sensitive clones from the killer F_1 (Kk) indicating a pair of nuclear alleles. Moreover backcross tests reveal that the sensitive F_1 's also carry the killer gene in heterozygous condition (Kk). It appears that there is an extranuclear substance (κ) which persists and multiplies in the presence of gene K , is lost after a few fissions in the absence of K , but cannot be produced, if absent, by action of K . Crosses between the killer line KK (κ) and a sensitive line KK (no κ) simulated pure cytoplasmic heredity. Later experiments (125) have brought out certain complications which seem to indicate that κ is taken up by the macronucleus and multiplies therein. Less exhaustive studies indicate that this mode of inheritance applies to all of eight other pairs of characters studied in the same variety. In other varieties of *Paramecium aurelia*, there is no indication of such semiautonomous extranuclear components.

Genes in relation to growth and differentiation.—Genetics is concerned with growth in two very different ways. Growth is naturally modified by a great variety of physiological conditions. It is not surprising that crosses of large and small varieties should usually reveal multiple factors. Powers (126) has studied the inheritance of a 56-fold difference in size of fruit in tomatoes. Results in F_1 , F_2 , and backcrosses conform fairly well to expectation under multiple factors with multiplicative effects but not at all under the hypothesis of additive effects. Smith (127) in a study of corolla length in derivatives of small flowered *Nicotiana Langsdorfi* and large flowered *N. Sanderae* compares various triploid and tetraploid types. He finds that chromosome replacements have more nearly

multiplicative than additive effects. Castle (128) presents data on certain genes of the mouse, recognized by effects on color, but with incidental effects on size. MacArthur (129) describes the effects of selection of strains of mice for large and small size which incidentally brought about differentiation in other characters (color, activity, relative lengths of ears, feet, and tail, and fecundity) presumably in the main because of multiple effects of the genes.

Growth, however, is in itself a process closely allied to heredity. Both consist of the multiplication of highly specific molecules. Step by step synthesis of the growth proteins, analogous, at a higher level, to the step by step synthesis of arginine in *Neurospora* discussed above presents difficulty (cf. Stern, 130). Autonomous duplication of the proteins in the cytoplasm is an alternative that also presents difficulties. If continuing along the germ line, it should result in cytoplasmic transmission of protein specificity, but as indicated by references cited here and by much earlier work, all studies of the genetics of specificity have indicated genic control. Another alternative is synthesis exclusively by nuclear genes (perhaps in the heterochromatin). Finally there is the possibility of cytoplasmic multiplication in the somatic cells subject to decay and ultimate nuclear control. The apparent active transfer of nucleic acid from nucleus to cytoplasm in cells that are rapidly dividing or about to do so may be pertinent (131). So also may be the nucleoprotein content of microsomes and mitochondria which Claude (132) suggests may be self-duplicating cytoplasmic bodies.

A related problem is the nature of the more or less permanent differentiation of cells in development, which from the standpoint of the cell as an organism constitute changes in cell heredity. The question whether such changes are nuclear (induced gene mutations in at least a formal sense) or are cytoplasmic, either as permanent changes in autonomous cytoplasmic components, or in the cytoplasm as a single self regulatory system, is of fundamental importance in physiological genetics but is a matter on which there is little evidence. The site of enzyme synthesis is, however, pertinent. The fact that isolated microsomes and mitochondria have various enzymatic properties (133) is at least compatible with the hypothesis that differentiation is cytoplasmic. Other observations, however, point to the nucleus as the site of enzyme synthesis in differentiated cells. Thus Krugelis (134) notes great alkaline

phosphatase activity in the salivary chromosomes of *Drosophila*. Isbell *et al.* (135) note the presence of appreciable amounts of B vitamins in isolated nuclei of beef heart and of mouse cancer, which finding suggests the presence of enzymes of which those vitamins are the prosthetic groups. Biesele (136) finds that chromosome size in normal rat organs varies in close parallelism with the total concentration of B vitamins (excluding inositol) while there is no such parallelism with total nuclear size, amount of cytoplasm, or development of plasmasomes. This does not apply to cancer cells (137) in which nuclei appear to be large because of multiplication of strands (indicated by considerable overt polyploidy but especially by multiplication of sets of plasmasomes) rather than because of the functional hypertrophy of large chromosomes in normal cells.

There are many genes whose effects seem to be restricted to particular kinds of cells—epidermis, nerve, sense cell, pigment cell, cartilage, etc.—but most of them are probably genes that find their substrate for action only in a particular class of differentiated cells rather than ones concerned with the differentiation process itself. Studies of pigment cells have already been considered. Other cases of tissue limited gene action will be considered in the next section. We may note here the detailed studies of gene controlled anemias in mice by Grüneberg. In one (138), recessives exhibit a flexed tail and often a white belly spot in addition to anemia at birth. The first generation of red blood cells, large, nucleate, produced in the yolk sacs are normal. These are replaced by smaller enucleate cells from the liver and later the bone marrow, which tend to be siderocytes, characterized by easily detached iron. The still smaller definitive red blood cells, which appear shortly after birth in normal mice are much delayed in appearance in the anemics and never fully replace the siderocytes in them. Another type of anemia associated with semidominant black eyed white has a wholly different basis: The anemia is of the macrocytic type as in human pernicious anemia. There are two mutant alleles with pleotropic effect of a puzzling sort (139).

Genes and morphogenesis.—All of the many papers on the genetics of morphological characters have physiological implications. A list of lethal and sublethal characters in farm animals (140) is instructive with respect to the nature of the more serious mutations.

In general, one notes a marked contrast between the simple direct relation of gene to character usually observed in the cases of antigenic specificity, or of single metabolic steps, and the complex and highly variable relations usually found between genes and morphological characters.

An autosomal recessive, determining the character "naked" in pigeons (141), may serve as an example of a gene which affects one tissue in a rather extreme but uniform way. More typical is the case of the character "ragged" in the fowl (142) also an autosomal recessive but expressed in only about 50 per cent of the cases and when expressed, varying from a slight reduction to complete elimination of primaries and secondaries. Microphthalmia in the mouse is another example of variable penetrance and expression. In this case, two major genes were indicated (143).

These are abnormalities of defect but the same principles apply to abnormalities of excess. Polydactyly of the fowl depends on an irregular semidominant (144). Variation in penetrance could be controlled to some extent. A moderate reduction in temperature during a critical period in incubation tends to suppress the character (145). Slifer (146) describes a mutation of *Drosophila melanogaster* which tends to bring out sex combs on the second and third legs of males as well as lengthening those which normally appear on the first legs. Here again there were thresholds and environmental effects (penetrance increasing from 9 to 93 per cent with increase in yeast in the medium). A well defined anterior-posterior gradient in occurrence and extent was brought out. Villee (147, 148, 149) has made detailed studies of the effects of temperature and genic modifiers on the effects of several other homoeotic genes of *Drosophila melanogaster*. Thus treatment of low grade aristopedia (ss^a-B) with cold (14°) during a certain period tends to increase the number of leglike segments of the arista, beginning at the base. Heat (29° to 35°) has the reverse effect on this series of alleles. The effects on proboscipedia are just the opposite, arista-like oral lobes after cold treatment, leglike ones after heat. An arista modifier (al) affects arista-like parts only. A number of genes with major effect on the legs (d, ds, fj, cg) modified the character of aristopedia while the latter in turn modified the effects of these genes on the legs. The effects of d, ds, fj, and cg had previously been studied embryologically by Waddington (150) who found unexpected and sometimes homoeotic effects of these genes

in combination. Glass (151) produced somewhat palp-like protrusions from the eye of *Drosophila* by x-ray treatment of embryos of a certain stock with morphologically normal eyes but shown to carry a favoring gene while other stocks lacked this and might carry a suppressing gene. Sawin (152) finds multiple factors to be responsible for homoeotic variation in the number of ribs and of presacral vertebrae of rabbits. The development of a prostate gland in female rats by inbreeding and selection, the reaction of which to hormone treatment has been discussed by Mahoney (153), is at least related to this class of variations. It is clear that these genes do not stand for the structures that replace normal ones, in the sense of complete determiners. They act rather as switches which call forth a more or less normal developmental reaction in a portion of the body in which this reaction is normally below the threshold.

While gene action seems highly localized in some cases, widespread effects are more common. A mutation of the mouse characterized by screw tail shows abnormalities also in sternum, pelvis, vertebral column, skull, and teeth (154). Another mutation of the mouse (155) has small ears and imperfect xiphisternum as well as small general size. Grüneberg (156) in connection with congenital hydrocephalus of the mouse, a case in which multiple effects appear to trace to one tissue, the cartilage, makes a distinction between spurious pleiotropism, of which this is an example, and possible genuine pleiotropism in which distinct primary actions of the same gene are involved. Another gene which he describes (157)—fidget—which combines abnormal behavior (head shaking, circling) with ultimate deafness, lesions of the cornea, and polydactylism, might seem an example of genuine pleiotropism but he holds that as a working principle it is desirable to assume that all cases are really spurious.

A renewed attack on the question of the prevalence of multiple effects of genes has been made by Dobzhansky & Holz (158). Visible mutations were induced in an isogenic stock by means of x-rays and studied for differences from type in respect to a seemingly unrelated character, the form of spermatheca. In most cases (14 out of 19) there were significant differences, though smaller ones than in an earlier study in which it was attempted to make a mutant isogenic by repeated backcrossing to type. They were greater, however, than observed by Schwab in an experiment similar to

the latter. The fact that all of the significant deviations from type were in the same direction suggests some general effect such as that of many mutations on viability and fertility.

Baumann & Landauer (159) find a correlation between occurrence of extra toes (usually asymmetrical) in polydactylous fowls and just those motor cells in the spinal cord concerned with innervation of the leg and foot. In view of experimental evidence, it is clear that the peripheral effect is primary.

Histological studies of the effects of genes such as Bar and eyeless of *Drosophila* on facet number and optic ganglia led to the conclusion that the effects on the latter are wholly dependent on the former by way of contributions from centripetal nerve fibers from the visual cells (160). Steinberg (161, 162) has carried the analysis of various eye mutants (Bar, Lobe alleles, eyeless) a step back to reductions in the number of cells entering into the eye discs, cells capable of forming either head chitin or facets depending on extrinsic and intrinsic factors. Waddington & Pilkington (163) have studied certain other genes of *Drosophila* with morphologically more abnormal effects on the eye, facet alleles, lozenge alleles, morula, and ophthalmopodia, the last of which carries us back to the homoeotic group. Abnormal histogenesis is attributed to abnormal folding rather than the reverse.

One of the most thoroughly studied cases of pleiotropism is that of the homozygous Creeper fowl. While the effect seems localized in the legs in heterozygotes, in homozygotes most of which die between 55 and 80 hours (prothanics) and all before hatching, the abnormalities are so general as to suggest some general metabolic disturbance. Most of the pathological symptoms of the prothanics, however, can be traced experimentally to one source (164), defect of the yolk sac circulation which is recognizable at 54 hours (23 to 27 somites). Defects of the eye (coloboma, virtual absence of sclera) which appear later may also depend on defective blood supply. Both normal and CpCp vesicles, transplanted to the orbit of a normal, developed normally (165). Both developed coloboma in an abnormal site (flank) of a normal embryo. A normal eye in the orbit of a homozygous Creeper showed all the defects of an eye of the latter. On the other hand, transplants from the leg and wing forming regions of five to eighteen somite embryos from CpcpXCpcp transplanted to noncreeper host, showed typical

phocomelia in 25 per cent (CpCp) in contrast with 75 per cent normal (Cpcp and cpcp). Apparently this aspect of the syndrome is localized too early to be due to circulatory defects (166).

Extreme apparent localization of effect in heterozygotes is associated with widespread effects in nonviable homozygotes in several tail abnormalities of the mouse. Dunn & Gluecksohn-Schoenheimer (167) found that a certain syndrome, simultaneous failure of post gut and urinary duct, sometimes including absence of kidneys, ureters, genital ducts, and bladder, may occur in a considerable number of genotypes with otherwise diverse effects.

Gene action in the earliest stages of development are of great interest. Poulson (168) finds that chromosome deficiencies involving the notch locus of *Drosophila melanogaster* bring about a characteristic distortion of the normal developmental pattern in which the entire nervous system shows hypertrophy associated with delay in differentiation. Robertson (169) has made a new study of the homozygous yellow mouse which he finds to develop normally through cleavage and blastocyst but to die after the trophoblast has come in contact with the uterine epithelium. There is slightly more development in the uterus of a nonyellow female.

Dunn & Gluecksohn-Schoenheimer (6, 170) have continued their studies of the effects of the various alleles of brachyury in mice. T/+ has a short tail, while T/T, which dies at ten and three-fourths days, lacks notochord and posterior portion of the body, $t^0/+$ and $t^1/+$ are normal, t^0/t^0 dies at about five days with no mesoderm or notochord, and t^1/t^1 dies still earlier before development of the embryo proper begins. The heterozygous combinations of these lethal genes can be produced by suitable matings. Combinations T/ t^0 and T/ t^1 are viable tailless mice while t^0/t^1 may be either viable with a normal tail or die early, with microcephaly but normal tail. The partially complementary action of these lethal alleles has already been referred to. The observation that genes, whose effect seems in general to be most severe on the posterior part of the body, should in one combination tend to produce a normal tailed microcephalic brings out again the point that the localization of gene effects is to be sought more in the properties of the organism than in the gene. The situation calls to mind that found in the experimental production of monsters by early treatment with deleterious agents. The dominant region in the physio-

logical gradient is that most capable of acclimatization to long continued treatment with low concentrations but is also the most sensitive to brief treatment with lethal doses. The microcephaly of t^0/t^1 under this view would indicate a short period of complete lack of complementarity of t^0 and t^1 while the predominantly posterior inhibition of T/T , the taillessness of T/t^0 and T/t^1 , and short tail of $T/+$ would indicate longer periods of less extreme metabolic defect.

The morphologic effects considered so far indicate that the array of genes determine a system with a high capacity for self regulation. Disturbances of metabolism, genic or environmental, often localized specifically in one tissue or another, are further localized in immediate effect by a threshold in a gradient of adaptive capacity. More widespread effects are determined by correlative influences. In another class of genetic changes, the disturbance of regulatory capacity takes the form of uncontrolled multiplication of particular cells. Russell (171) describes the genetics of a tumor of *Drosophila melanogaster* which depends on one principal gene but also on genic modifiers, with nongenetic factors responsible for a threshold. Gordon (172) is continuing his studies of melanomas of fish hybrids in which specific pigment genes with no abnormal effects within a pure species produce uncontrolled melanomas in the hybrids.

In a wholly different category is the observation of Wooley, Law & Little (173) of the restoration of high incidence of mammary carcinoma by injecting whole blood from a high tumor strain into mice tracing to this strain but exhibiting low tumor incidence for two generations following foster nursing on a low tumor strain. The "gene" in this case is neither in the chromosomes nor the cytoplasm of the germ cells.

Genes and behavior.—Many genes with effects on morphology necessarily affect behavior because of the nature of the morphological defects. A systematic study of the effects of mutations of *Drosophila melanogaster* on power of flight has been made by Williams & Reed (174), using a stroboscopic method. In some cases the reason for an observed effect was obvious but in others was quite obscure. The optomotor responses of various *Drosophila* mutants (175) could usually be correlated with morphology or color of the eye but not always. Scott (176) describes certain differ-

ences in behavior of *Drosophila* mutants, the reasons for which are not obvious. Keeler & King (177) find characteristic differences in temperament and behavior of color mutants that arose within a colony of Norway rats and so may be presumed to be pleiotropic effects of these genes.

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DEPARTMENT OF ZOOLOGY
THE UNIVERSITY OF CHICAGO
CHICAGO, ILLINOIS